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In the Office Action dated August 26, 2003, claims 1-24, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-24 have been canceled and new claims 25-48 have been added to the application.

The office action indicates that the first sentence of the specification should be amended to claim the benefit of an earlier application. The specification has been amended to reference the earlier PCT application.

The office action indicates that not all sequences have SEQ ID NOS. The specification has been amended to include SEQ ID NOS. A revised sequence listing is being prepared and will be filed shortly.

The office action indicates that "Epicurean" should be changed to "Escherichia". Applicants respectfully point out that "Epicurian coli" is the name used by Strategene for their competent cells. The specification has been amended to include the generic description "E. coli".

Claims 1-11 and 16-22 were rejected under 35 USC §112, second paragraph, as indefinite. Claims 1-24 have been canceled and new claims added to the application which do not include the language found indefinite. However, applicants point out that nucleic acid libraries can be prepared by partial restriction endonuclease digestion, whereby random fragments of the nucleic acid are obtained, but one skilled in the art would also realize that they can be prepared by shearing DNA by mechanical forces and refilling with Klenow, or they can be prepared with DNA synthetic fragments with a fixed sequence mixed with random nucleotides or they can even be prepared using synthetic random DNA sequences. Applicants respectfully contend the preparation of

libraries of random nucleic acids is known in the art. In view of this, applicants request that this rejection be withdrawn.

Claims 1, 3, 4 and 7-11 were rejected under 35 USC §102, as anticipated by Sawin. Sawin does not disclose an expression library of cDNA or cDNA fragments or the detection of polypeptides or parts thereof. Sawin generally describes the possibility of identifying genes, the expression product of which is located at a specific site of the organism after expression. Sawin's intent was to clarify to some extent which proteins are located in which structures and compartments of yeast cells. In contrast to Sawin, the present invention does not determine which protein is located where in the cell but identifies signals (small motif sequences within a protein or preprotein) which result in a protein being found in a particular localization of an organism. Using the present invention it is possible to identify genetic motifs which are not translated into a protein but are still localization sequences which can direct subcellular localization of any protein. Thus, the present invention goes far beyond Sawin's method. According to the present invention a sequence can be identified with a protein, which leads to the protein being transported somehow to a specific localization within the organism. Such a peptide sequence and the genes coding for it can then be used in connection with other proteins, so that a specific localization of a gene can be deliberately effected. The use of this method for identifying sub-structures in proteins which, irrespective of the protein, can bring about localization at a desired subcellular compartment is not described or suggested by Sawin.

Claims 16-19 were rejected under 35 USC §102, as anticipated by Gordon-Kamm. Claim 16 has been canceled and corresponding claim 41 added to the application. Claim 41 recites proteolytic cleavage sites between one or more of the

constituents of the fusion protein. Gordon-Kamm does not disclose such sites and thus applicants request that this rejection be withdrawn.

Claims 1, 5, 7-14, 16-19, 21 and 23 were rejected under 35 USC §102 as anticipated by Anderson. Anderson does not disclose an expression library of cDNA or cDNA fragments. In addition, Anderson's purpose was to search for bioactive peptides not to identify specific shorter sequences controlling subcellular localization of proteins in an organism which can then be used to direct other proteins or fusion proteins to a particular localization. Anderson used expression libraries of GFP fused to random and defined peptide libraries, to increase the cellular expression levels, decrease the cellular catabolism, increase the conformational stability relative to linear peptides, and to increase the steady-state concentrations of the random peptides and random peptide library members expressed in cells for the purpose of detecting the presence of the peptides and screening random peptide libraries. (col. 1, lines 7-13). Anderson states that " The invention provides methods of screening for bioactive peptides conferring a particular phenotype" (col. 2, lines 15-17). Anderson's goal was the "search of molecules that either inhibit or augment the biological activity of identified target molecules" (col. 1, lines 23-25) and Anderson states that "one particular problem with peptide libraries is the difficulty assessing whether any particular peptide has been expressed, and at what level, prior to determining whether the peptide has a biological effect." (col. 1, lines 28-31) and "This allows the creation of a peptide library that is easily monitored, both for its presence within cells and its quantity" (col. 2, lines 58-60). Thus, the aim of Anderson's method is to screen for bioactive peptides because GFP per se does not increase cellular expression levels or decrease the cellular catabolism.

It can help increase the conformational stability relative to linear peptides, and increase the steady-state concentrations of the random peptides.

Anderson uses the GFP to stabilize and monitor the bioactive peptide in terms of quantity and presence, not as a reporter protein to identify new peptides or polypeptides which drive the GFP to a specific subcellular localization. Though they speak about the use of targeting or binding sequences to allow the bioactive expression product to be limited to a specific localization or subcellular compartment (col. 11, lines 22-37), they do that to facilitate the effect of the peptide (col. 11, lines 4-21). They do not use the libraries to determine new localization signals as in the present invention.

Regarding the terms, "altered phenotype" or "changed physiology", which is the basis of Anderson's screening method, they say that "the phenotype of the cell is altered in some way, preferably in some detectable and/or measurable way" (col. 23, line 27-28), and they include "changes in the localization of one or more RNAs, proteins, lipids, hormones, cytokines or other molecules" (col. 23, lines 41-42). The bioactive peptide assayed produces those changes in cellular pre-existing components. The presently claimed screening method is not based on changes in pre-existing molecule localizations. The present invention produces a new protein with a localization signal. In view of the cancellation of claims 1-24 and the above discussion, applicants request that this rejection be withdrawn.

Claims 2, 5 and 6 were rejected under 35 USC §103(a) as unpatentable over Sawin in view of Stewart. As discussed above, Sawin does disclose a method for identifying sub-structures in proteins which, irrespective of the protein, can bring about localization at a desired subcellular compartment . Stewart does not cure this deficiency but is cited for the disclosure of cDNA and cDNA fragment libraries. In view

of the above discussion regarding the rejection over Sawin, applicants request that this rejection be withdrawn.

Claims 15 and 20 were rejected under 35 USC §103(a) as unpatentable over Anderson in view of Cha. Cha discloses proteolytic cleavage sites and does not cure the deficiencies in Anderson as discussed above. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 22 and 24 were rejected under 35 USC §103(a) as unpatentable over Anderson in view of Ahern. Ahern is cited for the disclosure of packaging of reagents and does not cure the deficiencies in Anderson as discussed above. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 25-48 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By 

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